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Genetic and Environmental Transactions Underlying the Association between Physical
Fitness/Physical Exercise and Body Composition

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Running head: Exercise and Body Composition

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Abstract

We examined mean effects and variance moderating effects of measures of physical activity and fitness on six measures of adiposity and their reciprocal effects in a subsample of the population-representative Danish Twin Registry. Consistent with prior studies, higher levels of physical activity suppressed variance in adiposity, but this study provided further insight. Variance suppression appeared to have both genetic and environmental pathways. Some mean effects appeared due to reciprocal influences of environmental circumstances differing among families but not between co-twins, suggesting these reciprocal effects are uniform. Some variance moderating effects also appeared due to biases in individual measures of adiposity, as well as to differences and inaccuracies in measures of physical activity. This suggests a need to avoid reliance on single measures of both physical activity and adiposity in attempting to understand the pathways involved in their linkages, and constraint in interpreting results if only single measures are available. Future research indications include identifying which physical activity-related environmental circumstances have relatively uniform effects on adiposity in everyone, and which should be individually tailored to maximize motivation to continue involvement.

Obesity has become an international concern in the last 20 years, as rates have increased dramatically. In the United States, they have soared beyond 30% and 10 more countries now clock in at over 20% (Organization for Economic Co-Operation and Development, 2011). Obesity reflects only the highest end of the population distribution of overall body fat that peaks at much more moderate levels. Relative frequencies at the highest levels have increased dramatically yet current rates of overweight still run considerably higher than those of obesity. Even in the range generally considered healthy, greater body weight is associated with coronary heart disease, diabetes, hypertension, sleep apnea, and high cholesterol (Haslam & James, 2005). Perhaps over-simplifying (Sørensen, 2009), development of excess weight is generally attributed to greater energy intake than expenditure, with both excess caloric consumption and insufficient physical activity contributing to the imbalance (French et al., 1994; National Institute of Health, 1998). Though obesity may impede physical activity, the stronger direction of influence appears to be from sedentary lifestyle to development and maintenance of overweight and obesity (Flegal, et al., 2010), and physical activity, particularly vigorous exercise, is considered to have important roles in preventing and overcoming overweight (Fogelholm & Kukkonen-Harjula, 2000; National Institute of Health, 1998).

Despite the source of the so-called obesity epidemic in our modern ('obesogenic') environment, population-based twin studies have consistently indicated the presence of substantial genetic influences on measures of measures of both body fat (Schousboe, et al., 2003) and physical activity (den Hoed, et al., 2013). At the same time, there is considerable evidence that regular physical activity may suppress genetic variation in body weight at population level (e.g., Ahmad, et al. 2013; Heitmann, et al., 1997; Karnehad, et al., 2006; Kilpelainen, et al., 2011; McCaffery, et al., 2009; Rankinen & Bouchard, 2012; Silventoinen et al., 2009; Williams, 2011), indicating complex transactions between genetic and environmental influences (Johnson, 2007). This evidence has come from studies of both individual genetic polymorphisms and quantitative genetics that have estimated genetic influences in the aggregate. Increasing suppression of genetic variance in body weight with greater levels of physical activity suggests that as habitual exercise levels get more intense, either the people who tend to engage in higher levels are increasingly similar with respect to genes involved in body fat; or the more intense the habitual exercise level, the more it affects everyone's body fat levels similarly, regardless of genetic background; or some combination of the two.

A contributing factor involves the fact that individual behavioral choice is involved in exercise levels but not directly in degrees of body fat. That is, everyone has some unstructured time and, absent acute disability, can choose whether to spend it sitting around or doing something more physically active. The same kind of choice is not available with respect to body fat. We do, however, exert some behavioral control over body fat through lifestyle choices, but they affect it only indirectly, probably primarily via amount and type of food consumed and level of physical activity, but possibly a host of other factors. Because these lifestyle choices have some roots in genetically influenced cognitive and personality traits (Turkheimer, 2000), people with similar habitual exercise levels may be relatively similar with respect to the genes involved in propensity to exercise as well as those involved in body fat. To the extent that physical activity has environmentally causal effects on body weight, the genetic influences on propensity to exercise will tend over time to 'bleed into' those on body weight, creating genetic correlation, or the appearance of genetic influences common to propensity to exercise and body fat. This is the reason that genetic correlation is often interpreted as evidence of gene-environment correlation when one of the variables involved is considered 'environmental'. Such genetic correlations will arise even in groups of people who all have the same position on the 'environmental variable' (and thus no 'variance' in that characteristic), as long as that position is influenced by large numbers of both specific genes and specific environmental factors so that there are many pathways through which any individual could reach any particular 'environmental' variable level (Abarbanel et al., 2009). Such multiplicity of pathways is highly likely to be the case with propensities to both exercise and body fat. The causal influences could run in the opposite direction as well, for example when sports programs identify children with specific body builds and recruit them for sports training, or when excess body weight makes physical activity more difficult and less pleasant, thus decreasing motivation to engage in it.

But genetic correlation could arise in another way. That is, it could be the case that some genetic variants specifically contribute both to propensity to develop body fat and preference for sedentary lifestyle, or resistance to formation of body fat and preference for physical activity, that is, so-called pleiotropy. This is the mechanism often assumed in the literature for observed genetic correlations, but it is not necessarily the most likely one, though pleiotropy may co-exist with environmental sources in creating the genetic correlations often observed. Lifestyle choices create environments, but they almost certainly have their effects on body fat by moderating expression of the

genes involved. These may be genes on which humans do not tend to vary as well as genes on which they do. To the extent the genes involved do not tend to vary among humans, we should expect everyone to respond similarly to any given level of habitual exercise. In this case, genetic correlations may be low.

These possible patterns of causal relations apply to shared and non-shared environmental influences as well. Distinguishing among all three can help to reveal how physical activity, or the lack thereof, is involved in maintenance of body weight, and thus to design programs that can be effective in encouraging physical activity that can prevent obesity. For example, if we knew that physical activity has its effects in minimizing weight gain primarily by suppressing expression of genes involving fat development on which humans do not tend to vary, relatively uniform policies and guidelines to encourage physical activity may be appropriate. In contrast, if there are genetic variants that contribute to both development of obesity and preference for sedentary lifestyle, there would be public health and economic advantages to developing policies and programs intended specifically to motivate those more vulnerable to obesity to get more exercise than many of them would prefer. This is probably considerably more challenging, especially in cultures that value individuals' freedom to choose their own lifestyles.

The purpose of this study was to explore the genetic and environmental transactions between measures of physical activity and body fat to begin to distinguish among the possible genetic and environmental pathways involved in their associations. We did this with respect to aggregate sources of influence, rather than with respect to individual genetic polymorphisms. Results of such study can only be suggestive. At present, however, we have a basic understanding that obesity results from long-term excess of energy intake over expenditure, but also an awareness that its development results from very small day-to-day imbalances that involve not only measures of energy intake and expenditure at the levels we can track, but also metabolic adaptations to those levels and variations in them (Shook, Hand, & Blair, 2014; Sorensen, 2009). These can show both genetically and environmentally influenced consistency across populations, and genetically and environmentally influenced individual differences. The models we used can offer hints about these processes.

We expected to replicate the basic observations of prior studies that physical activity suppressed genetic variance, but our study extended prior quantitative genetic studies in three ways. First, our study had the advantage of access to six measures related to body fat and adiposity, and

these measures were objectively recorded rather than self-reported. The most accurate measures of body fat, including DXA and MRI scans, tend to be rather expensive and somewhat inconvenient, so most studies have relied on cheaper, simpler, but inevitably more approximate measures. Doing so makes it important to examine several such measures to minimize the possibility that limitations of measurement accuracy in any one measure have affected results. Moreover, the various indirect adiposity-related measures in common use reflect characteristics of body structure that appear to tap different aspects of metabolic function that may indicate either different physiological responses to physical activity or different forms of health risk, or both. Thus, comparison of results from several different measures may provide insight not just about their robustness, but also about how physical activity could have different influences on different aspects of body structure and health.

Second, we had the advantage of access to rather robust measures of habitual physical activity from two perspectives. One perspective from which to measure habitual physical activity is to ask people to report the frequency and intensity and nature of their activities. This generates a direct assessment of actual activity, but it is subject to all the distortions involved in self-reports, including, probably especially in this case, the subjectivities in interpreting intensity of activity. Many studies have made use of responses to very simple items such as number of days per week of activity only very loosely defined, compounding the problems of measurement imprecision. Another approach is to measure the result of physical activity in the form of physical fitness. This reflects physical capacity response to habitual (or prior) activity rather than activity itself, and people vary in fitness response to any given level of activity, as well as in extent of loss of fitness with cessation or reduction of regular activity. It is also less convenient to assess, but doing so is generally considerably more precise and less subjective. Thus, the two activity measures available to us positioned us to obtain information both about extent of robustness of results and possible differences in nature of effects.

The third way in which we extended prior quantitative genetic studies was methodological. Such studies have either inferred suppression of genetic influence on adiposity with greater physical activity indirectly based on participant reports of parental weight status (e.g., Williams, 2011), or made use of a model that estimates only genetic and environmental influences unique to the trait considered outcome (e.g., Silventoinen, et al., 2009; see Purcell, 2002), in this case some measures of adiposity, thus limiting considerably the ability to explore the causal possibilities discussed above. We made use of a much more powerful model that considers both possible genetic and

environmental influences common to physical activity and adiposity and unique to each of them (Johnson, 2007; Purcell, 2002), and compared results to those from recently recommended possible alternative models (van Hulle, Lahey, & Rathouz, 2013). In doing so, we considered possible effects of both physical activity on adiposity and adiposity on levels of physical activity. In particular, all three of the ways in which we extended prior quantitative genetic studies applied to Silventoinen, et al. (2009), which made use of the same sample as we did.

METHOD

Participants

Study participants came from the GEMINAKAR sample, which was drawn from the nationwide Danish Twin Registry established in 1954. The first such registry to be established, the Registry includes twin births from 1870 to 2010, with almost 90,000 twin pairs registered to date (Skytthe, et al., 2013). The GEMINAKAR study was designed specifically to explore how genetic and environmental influences are involved in associations between lifestyle factors such as diet, smoking, and exercise, and endophenotypes of the metabolic syndrome. The sample consisted of 756 complete twin pairs (311 monozygotic [MZ]; 314 same-sex dizygotic [DZ]; 131 opposite-sex DZ; 783 women; 729 men) examined between August 1997 and November 2000 (Benjamin, et al., 2007; Hasselbalch, et al, 2008; Schoesboe, et al., 2004). At the time of examination they were aged 18-67 years (median 38.0 years), were not pregnant or breastfeeding, did not abuse alcohol or drugs, had not been diagnosed with diabetes or heart disease, and did not have other physical conditions that precluded participation in the assessment that included a bicycle fitness test. Twin zygosity was determined using DNA-based microsatellite markers (AmpFISTR Profiler Plus Kit; PE Applied Biosystems, Perkin Elmer, Foster City, CA, USA). The twins underwent detailed clinical examinations and blood sampling in two identically equipped locations in Denmark (Odense and Copenhagen). They had been fasting for 12 hours when undergoing to examinations, but had a light meal before having to do the bicycle test. Trained medical examiners administered the anthropometric measures of height, weight, and waist and hip circumferences used in this study, applying standardized protocols. The GEMINAKAR participants were typical of the overall Registry in BMI, except that the Registry did at the time include some participants who would not have been eligible due to obesity severe enough to preclude the bicycle fitness test (mean=24.4, sd=3.5, Skew=.9 in GEMINAKAR; mean=24.5, sd=4.0, skew=1.6 in the Registry).

Measures of Adiposity

Six measures of adiposity were available, including Body Mass Index (BMI), waist-hip ratio (WHR), waist-stature ratio (WSR), body fat percent, fat mass, and lean mass. The descriptions that follow are intended to highlight the vagaries and different underlying assumptions in these commonly used measures, and thus the reasons that examining as many as possible is important. BMI is defined as mass in kilograms/(height in meters)². It thus adjusts body weight for variation in a readily-available approximation of body surface area, thus taking into consideration both height and some approximation of the relatively larger bone circumference that tends to go with greater height. In adults, BMI less than 18.5 is generally considered underweight, BMI between 25 and 30 overweight, and BMI in excess of 30 obese. Mass generally increases not with the square of a linear measure as does surface area, but with the cube of the linear measure, so larger bodies have higher BMIs even when two bodies of different overall sizes are proportioned identically. As muscular tissue weighs more than fat tissue of comparable volume, BMI tends to overestimate body fat in well-muscled people such as athletes, while underestimating it in those with less muscle, who are often also less physically active. The distortions involved can be considerable. For example, athletes with BMIs falling in the overweight category can have body fat percentages in the 10-15% range, below those of most sedentary people with BMIs considered normal (Kruschitz, et al. 2013). Physicians take this kind of individual variation into consideration, however, and do not recommend weight loss to patients in this situation.

Waist-hip ratio (WHR), or the ratio of waist to hip circumference, is used as an indicator of health by the World Health Organization (WHO). The idea is that, size for size, greater adiposity around the waist is an indication of vulnerability to heart disease, diabetes, hypertension, and, in the elderly, mortality. WHO guidelines specify WHRs in excess of .9 for men and .85 for women as indicative of abdominal adiposity. This measure reflects primarily body structure and fat distribution rather than overall adiposity. It thus captures something different from the other measures, as there appear to be individual differences in both the relevant underlying body structure and tendency for excess weight to congregate around the waist that are independent of overall body fat (Lindgren, et al., 2009). This is also indicated by associations with fertility and reproductive health in both sexes (e.g., Singh, 2002; Marlowe, Apicella, & Reed, 2005). In general, WHR guidelines tend to classify more people as overweight or obese than do BMI guidelines, especially for women. Waist-stature

ratio (WSR) is the ratio of waist circumference to height. It better reflects overall body size than does WHR, but does not capture fat distribution in ways that appear meaningful. Still, at least one large study found it to be a better indicator of cardiovascular risk than BMI (Schneider, et al., 2010). As a general health risk threshold, .5 has been suggested (Browning, et al., 2010). Because they depend on waist circumference, WSR and WHR are subject to similar distortions as measures of adiposity and health risk: poor fitness level appears to contribute particularly to accumulation of fat around the waist, thus affecting the association between waist circumference and body fat (Janssen, et al., 2004), and measurement error tends to increase with waist circumference due to greater difficulty in locating the 'natural waist' in those with greater adiposity. There are also variations in typical body fat mass and body shape with ethnicity that may not reflect variation in health risk to the same degree.

Body fat percentage is the ratio of total fat mass to total body mass. Some fat is essential to maintain life and reproductive function, with women requiring more than men to support childbearing and other hormonal functions. In men, 2-4% fat mass is considered essential; for women essential fat runs 10-13%. Thus, given population mean levels that often run 30% for women and 20% for men, the clear majority of body fat in both sexes is considered non-essential. This 'storage fat' accumulates in adipose tissue. Some of it protects the internal organs in the body trunk, so recommended total body fat percentages are higher than the levels considered essential. Levels over 32% for women and 25% for men are generally considered obese. Serious athletes usually run levels just higher than those deemed essential, and body fat percentage is generally negatively associated with fitness throughout the population. Both anthropometric and direct estimation methods are available, with anthropometric measures being much cheaper and easier to administer but also less accurate. This study made use of bioelectrical impedance analysis, which is a direct method, but one of the cheapest and least accurate ones. The method is based on the resistance presented by the body when a small electrical current is sent through it. The greater proportion of salt water in muscle mass than fat mass facilitates electricity conduction, making it possible to estimate the needed ratio of fat mass to total mass. Sources of inaccuracy in the result stem from the specific instrument used, the formula used to translate the observed electrical resistance to body fat percent, and subject factors such as body frame shape and recency of exercise or food or drink consumption. In conjunction with body mass, body fat percentage can be used to estimate body fat and lean mass. Due to equipment failure that took some time to repair, these measures were available only for 1039 of the total 1512 participants.

Descriptive statistics for all the adiposity measures are shown in Table I. Few participants' data fell consistently in the ranges considered obese, but many would be considered overweight.

Measures of Physical Activity

Participants completed a bicycle fitness test to measure VO_2max , or maximal oxygen consumption during exercise, a measure of physical endurance capacity. The test was carried out using a stationary bicycle mounted with an ergometer to measure energy expenditure. The participant was instructed to start pedaling at a workload of 35 watts, and to increase this by 35 watts every two minutes until the workload could no longer be sustained. The highest workload reached and the seconds over which this workload was maintained, age, sex, and weight were used to measure VO_2max in liters/(kg-minute).

Participants also completed an extensive series of questions about their physical activity levels. They reported whether their jobs were primarily sedentary, involved some standing and walking, considerable walking and some lifting, or heavy manual labor, whether any lifting involved was heavy or relatively light, and rated their leisure-time physical activity similarly. In addition, they reported the numbers of hours per day they walked and cycled in summer and winter as 'never', '0-30 minutes', '30-60 minutes', '1-2 hours', or 'more than 2 hours', and rated the speed with which they did so as 'slow', 'normal', 'brisk', or 'very brisk'. Finally, they reported how many minutes per week they engaged in sports including gymnastics, running, swimming, tennis, football/soccer, handball, 'fitness studio', etc. We used this information to estimate average daily Metabolic Equivalent of Task (MET) unit expenditure for each participant based on Ainsworth, et al. (2011). Measured as kcal/kg/hour, METs reflect the ratio of metabolic rate while engaging in some specific task relative to resting metabolic rate. They can also be defined as oxygen uptake in ml/kg/minute, thus limiting them by VO_2max . As with the adiposity measures, any scale such as the one we created is subject to a number of limitations. Published MET values for specific activities are overall averages derived under experimental conditions from specific samples. Actual levels of energy expenditure depend on intensity of effort, amount of mass that must be moved, and fitness; and expenditure under natural conditions can differ from those in the experimental conditions even for the same person. Moreover, there are substantial individual differences in resting metabolic rate per unit of body weight. All self-report measures are subject to distortions due to differences in perceptions, memory and estimation accuracy, and motivation to leave positive or negative impressions. Despite all this, our measure was

considerably more comprehensive than those used in many studies of physical activity levels, which have often relied on single questions answered on 4-5-point scales (e.g., Silventoinen, et al., 2009).

Descriptive statistics for the physical activity and fitness measures are also shown in Table I. The average cycle fitness level of 34.34 in the sample was about what would be expected for an untrained group of healthy male and female adults, with such males tending to run 35-40 ml/(kg-min) and females 27-31 (Heywood, 1998). The average daily MET expenditure average of 3283.1 was equivalent to about 12 hours per day spent sleeping or watching TV and about 12 hours per day doing the equivalent of riding a stationary bicycle very slowly and leisurely. Almost 30% of the sample reported that their walk pace was 'brisk' or 'very brisk', and over 20% reported regularly cycling briskly or very briskly. Almost 40% reported at least light leisure physical activity at least 4 hours per week, and about 35% reported that their jobs involved at least extensive walking and some lifting. Over 50% reported that they walked at least 90 minutes per day, and 10% reported cycling at least that amount. Thus, many appeared to be the equivalent of leisurely active throughout the day, with some periods of more intense activity.

Analysis

The standard quantitative genetic twin model relies on the assumption that variance can be attributed to additive genetic influences (A) shared environmental influences that make co-twins similar but differentiate among twin pairs (C), and non-shared environmental influences including measurement error that make people different from each other regardless of twin zygosity or family membership (E). Because MZ twins share effectively all their genes and DZ twins share on average 50% of their segregating genes, higher correlation between MZ twins than DZ twins indicates additive genetic influences. Shared environmental influences are indicated by DZ correlation greater than one-half the MZ correlation, and non-shared environmental influences by MZ correlations less than 1.0. There is evidence that some of the genetic influences involved in body weight may be nonadditive (e.g. Stunkard, Harris, Pedersen, & McClearn, 1994), In the model, this would show up as MZ twin correlations that are greater than twice the DZ correlations. There was evidence of this only for MET, but any such nonadditive influences are confounded with also-possible assortative mating for body weight that would act to make DZ twins more similar than expected. Given the little evidence for nonadditive genetic influences in these data, we made use of the standard model.

This univariate model can be extended to estimate genetic and environmental contributions to covariance between two traits. The extended model provides estimates of A, C, and E influences on one trait that also influence the other, thus creating their covariance, and estimates of A, C, and E influences that contribute only to the latter trait. The standardized covariance attributable to genetic influences provides an estimate of the genetic correlation, and the shared and non-shared environmental correlations can be estimated similarly.

The primary model we used had one additional essential extension. The models described so far provide estimates of A, C, and E influences applicable to the population at large assuming there are no interactions among the sources of influence and that the magnitudes of influences are constant throughout the population. We used a model that relaxed these assumptions to examine possibilities that the variance components differed in different parts of the population, and in particular that such differences in measures of adiposity were associated with levels of physical activity and vice-versa. Figure 1 diagrams the model. The parameters indicating moderation that were of particular interest in this study are b_1 through b_6 . This model measures only variance components; it does not account for mean level differences. Yet much of the reason for implementing such a model is to understand the processes underlying the negative association between physical activity and adiposity that results in higher mean levels of measures of adiposity in less physically active groups. Thus, it is important to integrate analyses of mean level differences with results from this model.

Because the model does not explicitly account for mean differences, it cannot distinguish clearly between nonlinear main effects on mean levels that do not moderate variance and moderation of covariance (Rathouz, et al., 2008). This possibility can be evaluated by fitting models of nonlinear main effects on means and evaluating significance of the nonlinear terms (van Hulle, Lahey, & Rathouz, 2013), and we did this wherever we found evidence of such possible confounding in the form of significant moderating effects of parameters b_1 , b_2 , or b_3 .

We implemented the model shown in Figure 1 in Mx software (Neale, et al., 2003), using maximum likelihood estimation so that all available data were included, regardless of co-twin data availability. Because we were interested in variance differences as well as differences in means, we estimated absolute genetic and environmental variance components rather than proportions of variance components to total. To avoid confounding scale of measurement with moderation of variance (Falconer & Mackay, 1989), we checked that all variables were reasonably normally

distributed and that partitioning in equal intervals along their ranges revealed no trends in variance. We allowed parsimony to dictate the results presented by testing the significance of terms indicating variance-moderating effects (the b coefficients in Figure 1) and dropping them when doing so did not reduce model fit. To maximize potential power and because interpreting results is more straightforward when there is no moderation on variance common to moderator and phenotype, we first attempted to drop parameters b_{1-3} , and only retained any of them if this was not possible. Following that, we considered the remaining three moderating parameters individually. We evaluated model fit using the information theoretic fit statistics Akaike's Information Criterion (AIC; Akaike, 1983) and Bayesian Information Criterion (BIC; Raftery, 1995). We dropped non-significant moderating terms to focus attention on the most important effects rather than to reject the potential existence of smaller moderating effects that happened not to be significant here. All variables were adjusted to remove effects of age and sex (McGue & Bouchard, 1984). We focused on significance of the moderating parameters as indicated by model fit rather than confidence intervals in interpreting models, as the estimated genetic and environmental influences varied with level of moderator. Moreover, the genetic and environmental correlations were not estimated directly but were based formulas using the estimates of the genetic and environmental variance components and moderating parameters. As noted by Medland, et al. (2009), this makes their estimation both less precise and less meaningful than when these correlations are estimated directly.

RESULTS

Table II shows the phenotypic correlations among the study variables. As would be expected, there were substantial age and sex effects. Older participants tended to be shorter and heavier, with larger waist circumferences, greater body fat percentages, and lower activity levels (except for walking). Women tended to be shorter and lighter than men, with greater body fat percentages and lower activity levels (except for cycling). As noted above, we removed these effects prior to our primary analyses. We did this because we did not have sufficient power to examine the sexes separately, let alone the possibility of different patterns of moderating effects in different age ranges. Future studies should address these topics. Raw correlations among the measures of adiposity varied widely, ranging from -.09 for WHR and Body Fat Percent to .91 for BMI and Fat Mass. Cycle Fitness was correlated -.22 to -.55 with the adiposity measures, but Total MET had much lower correlations, ranging from -.03 to .07. The two activity measures correlated .22.

To provide supplementary information that could help to understand the moderating effects we observed, we ran Cholesky models to estimate the extents to which the adiposity measures shared genetic and environmental influences. Results are shown in Table III. Genetic correlations ranged from .26 for Lean Mass with WSR to .95 for Fat Mass with Body Fat %. Shared environmental correlations ranged from .05 for Body Fat % with WHR to 1.00 for WSR with BMI. Non-shared environmental correlations ranged from .41 for Lean Mass with WHR to .98 for Fat Mass with BMI. There was a clear tendency for similar measures to have high correlations, and in general, the correlations paralleled the phenotypic correlations. We also estimated the genetic and environmental correlations between the activity measures. The genetic correlation was .28, the shared environmental -1.00, and the non-shared environmental .27.

Twin correlations are given in Table IV. All variables showed substantial evidence of genetic influence, and, with the exception of Total MET, evidence of shared environmental influence as well.

Models involving Cycle Fitness. Table V shows fit statistics for the models involving Cycle Fitness, with Cycle Fitness considered a moderator of each of the various measures of adiposity in the top panel, and considered the outcome phenotype in the bottom panel. Regardless of direction, some degree of moderation of variance was indicated for most of the adiposity measures, suggesting reciprocal causal influences in their association. Here, as for all the analyses, though power to detect effects was somewhat lower for Body Fat Percent and Fat and Lean Mass due to reduced availability of data for those measures, the model-fit statistics did not indicate reduced ability to detect effects. The existing literature contains many papers reporting studies that have made use of this model in samples of similar size, though few have reported the genetic and environmental correlations in the detail reported here. As indicated by some generally replicable effects when phenotypes are similar, there is adequate power to detect meaningful effects in samples of this size, and the model-fit statistics offered no evidence that lack of power impeded ability to detect moderating effects.

As indicated in the second-to-last row of each panel of the table, the sources of moderated Cycle Fitness variance differed with adiposity measures somewhat, as did the sources of variance in measures of adiposity moderated by Cycle Fitness, suggesting some differences in their causal mechanisms. Results of testing the alternative models of nonlinear main effects on means (van Hulle et al., 2013) are indicated in the last line of the panel. Most of the moderating effects appeared to suggest true variance moderation rather than nonlinear main effects, as either there was no apparent

moderation of variance common to Cycle Fitness and adiposity measures, or quadratic main effects terms were not generally significant. For Cycle Fitness as moderator, the one exception to this was Lean Mass, and the pathway of either direct cause or variance moderation appeared to be shared environmental. For Cycle Fitness as outcome, competing nonlinear models were indicated for WHR, WSR, and Body Fat Percent, with genetic, shared environmental, and genetic sources respectively indicated as the pathways.

Table V also shows model fit statistics for Cycle Fitness considered as a moderator of MET, and vice versa. These models were run to assess the possible power of variance-moderating effects of either one of them on the other to influence results from the other models. This did not appear to be of further concern, however, as no moderating effects were apparent.

Figure 2, based on results from the best-fitting model in the top panel of Table V, shows that there was considerable consistency in the ways that Cycle Fitness moderated the various measures of adiposity. In general, there was less variance in adiposity when Cycle Fitness was high. This indicated that Cycle Fitness' effects in minimizing adiposity became stronger and more uniform across individuals with higher levels of it. In all cases non-shared environmental variance was less when Cycle Fitness was high, so some of the greater strength of effect took place by suppressing individual differences in adiposity created by non-shared environmental influences. In general, shared environmental variance showed the same pattern as non-shared environmental variance, but genetic variance was sometimes moderated and sometimes not. Cycle Fitness' moderating effect on genetic influences on Body Fat Percent was clearly different from those on the other adiposity measures. It acted to increase rather than reduce genetic variance at higher levels of Cycle Fitness, to the point that overall variance was greater there than lower levels, despite decreasing non-shared environmental variance with higher Cycle Fitness. WHR also clearly showed a very different variance pattern than the other measures of adiposity. It had much greater shared environmental influences overall, and they too were greater at higher than lower levels of Cycle Fitness.

Mean levels of the adiposity measures across the range of Cycle Fitness, along with the genetic and shared and non-shared environmental correlations, are displayed in Figure 3. Again, these are taken from the best-fitting models in the top panel of Table V. The mean level trends were very consistent in indicating lower levels of adiposity with higher levels of Cycle Fitness, as would be expected. The various correlations, however, were not consistent from measure to measure even in

direction. For example, the genetic correlation between Cycle Fitness and WHR ranged from about -.6 at 2 standard deviations below mean Cycle Fitness to about .3 at 2 standard deviations above, while the genetic correlation between Cycle Fitness, and Body Fat Percent ranged from about 0 at 2 standard deviations below mean Cycle Fitness to about -.8 at 2 standard deviations above. The non-shared environmental correlations showed similar lack of consistency, but it did not run parallel to the inconsistency in the genetic correlations. Overall, the non-shared environmental correlations were smaller in absolute magnitude than the genetic correlations, probably mostly reflecting the presence of measurement error there. The shared environmental correlations had the most dramatic patterns, despite the fact that there was little shared environmental variance in most of the adiposity measures. For example, the shared environmental correlations ranged from -1.0 to 1.0 across the range of Cycle Fitness for BMI and Fat and Lean Mass. These kinds of swings in shared environmental correlations observed here are quite common in applications of this model, though most papers have not reported these correlations in sufficient detail to reveal this. They appear to indicate main effects on mean levels that do not affect variance and are not directly modeled, as noted above. We address these topics further in the Discussion.

Analogous to Figure 2, Figure 4 shows how the various measures of adiposity moderated Cycle Fitness, based on the best-fitting models from the bottom panel of Table V. Overall, the patterns closely resembled those for Cycle Fitness as moderator of adiposity. That is, variance in Cycle Fitness was lower when adiposity was high, indicating that adiposity's effects in limiting Cycle Fitness became stronger and more uniform across individuals with higher levels of it. The sources of the moderating effects of the various measures of adiposity on Cycle Fitness tended to differ, however, as did the extent of moderating effects. For example, Body Fat Percent showed only much smaller moderation of variance, transmitted genetically. In contrast, high WSR sharply restricted all forms of variance in Cycle Fitness, while WHR sharply restricted only shared environmental variance in Cycle Fitness. The one panel in Figure 4 that differs from the others is Lean Mass as moderator, but this overall result was not inconsistent with the others, as greater Lean Mass is associated primarily with greater body size and only secondarily with relative proportions of lean and fat tissue unless adiposity is extreme. Because of this, the shared environmental moderating effects indicated primarily that Lean Mass' effects in promoting Cycle Fitness were somewhat stronger and more uniform in people of smaller body size.

Figure 5 displays mean levels of Cycle Fitness across the ranges of the various measures of adiposity, along with the genetic and shared and non-shared environmental correlations based on the best-fitting models from the bottom panel of Table V. Again, it was very clear that adiposity was associated with lower Cycle Fitness, but the pathways and processes differed with adiposity measure. The genetic and non-shared environmental correlations were more consistent than when Cycle Fitness was moderator, both with each other and across the various adiposity measures. Again, it was the shared environmental correlations that were generally strongest, however. WHR was an exception to this.

Models involving MET. Like Table V, Table VI shows fit statistics for the models involving MET, both when MET was considered a moderator of each of the various measures of adiposity, and when it was considered the outcome phenotype. Unlike Cycle Fitness, however, there were relatively few moderating effects and all but one occurred when MET functioned as moderator rather than phenotype. Again, the only phenotype for which a nonlinear main effect appeared a plausible competing explanation was Lean Mass. Perhaps because of this, Lean Mass was the one body measure that showed variance-moderating effects on MET. In addition, with the exception of Lean Mass, all the observed variance-moderating effects of MET on adiposity measures involved genetic variance unique to the adiposity measures, not shared with MET. This was consistent with the low correlations between the adiposity measures and MET.

Figure 6 shows the moderating effects of MET on the measures of adiposity on which they were observed, based on the best-fitting models from the top panel of Table VI. The difference in pattern for Lean Mass from the others is clear in the decreasing red shared environmental variance with greater MET. Figure 7 shows mean levels of the variance-moderated measures of adiposity across their ranges, along with the genetic and shared and non-shared environmental correlations, again based on the best-fitting models from the top panel of Table VI. The relatively flat mean lines reflect the low correlations with MET, but Lean Mass' correlation was much higher (.22; the next strongest was .07). The non-shared environmental correlations were very low and stable across the range of MET, and the genetic correlations were not much stronger. In contrast, the shared environmental correlations were consistently -1.0. We address the implications of this in the Discussion.

Because only Lean Mass moderated variance in MET, the primary value of the specific results of the moderation models was to indicate degree of consistency of estimates of genetic and environmental influences on MET in the presence of the variance moderating variables. We thus do not present the results from the models in the bottom half of Table VI graphically. Instead, the estimates of genetic and environmental variance in MET and the genetic and environmental correlations with the adiposity measures resulting from these models are presented in Table VII. Estimated variance components in MET were quite consistent. The most variable was genetic variance in MET, which ranged from .34 to .39 for all adiposity measures except Lean Mass. For Lean Mass, it was .27. The genetic and environmental correlations provided some insight regarding the very low phenotypic correlations, shown in Table II, which ranged from -.06 to .07, as well as for the relatively low genetic variance estimate for MET when modeled with Lean Mass. The genetic correlations were uniformly positive, but the shared and non-shared environmental correlations were negative (where there was shared environmental variance), with the exception of the shared environmental correlations between MET and Lean Mass. Thus, the genetic and environmental influences common to MET and the adiposity measures offset each other. The genetic and non-shared environmental correlations were at best moderate, but the shared environmental correlations were strong where defined. There was so little shared environmental variance, however, that this had little effect on the phenotypic correlations.

DISCUSSION

In this study, we examined how two measures of physical activity moderated six measures of adiposity in a sample of adult Danish twins. We replicated the basic observations of prior studies that physical activity suppressed variance in adiposity, but the variance that was suppressed was not always genetic. The use of both multiple objectively-recorded measures of adiposity and two rather robust measures of physical activity extended prior research by allowing comparison of results derived from measures that have different limitations as approximations of adiposity and physical activity. More importantly, however, our analysis was based on a much more powerful model that considers both influences common to adiposity and physical activity and unique to each of them (Johnson, 2007; Purcell, 2002), and compared results to those from recently recommended possible nonlinear-main-effect alternatives (van Hulle, Lahey, & Rathouz, 2013). We also examined both implicit causal pathways from physical activity to adiposity and from adiposity to physical activity and

differences in mean levels with levels of moderator, making possible much richer interpretation of likely underlying processes. Although these interpretations are of necessity speculative and could apply relatively narrowly to this sample even if accurate here, they open considerable possibilities for further research and ultimately interventions to prevent obesity. Before considering these interpretations, however, we discuss the inevitable limitations of this study.

Study Limitations

Our sample was of moderate size, though it was drawn from a sample highly representative of its population. It was also quite representative of that sample, though it did not include any of its most obese participants. Like most study samples, it was specific to one country and time period, limiting generalizations to others. In this case, the sample was Danish. Denmark does have rather low obesity rates and its population is more likely to cycle or walk for transportation than those in some other economically developed countries with higher rates of obesity, particularly the United States. In addition several of our measures of adiposity and one of our measures of physical activity had substantial amounts of missing data. This was due to equipment failure so data could be considered missing at random (though not completely so) and model parameter estimates unbiased (Little & Rubin, 1989), but it still limited power to obtain precise estimates of those parameters. We also constrained estimates of moderating parameters to 0 when we could do so without loss of model fit. This means that we could have missed moderating effects that might have been significant with a larger sample or more complete data. Moreover, our model relies on the assumptions that our participants' parents did no assortative mating for either adiposity or physical activity, that MZ and DZ twins experienced within-pair familial and other shared environmental circumstances in the same ways, and that genetic and environmental influences can be considered independent and additive, except for the kinds of dependencies and transactions specifically modeled.

Moreover, our MET measure relied on self-reported physical activity, though it surveyed areas of activity rather extensively, requesting reports of both frequency and intensity of activity at work and at leisure and for transportation, as well as involvement at leisure in specific activities. Such measures are always subject to inaccuracy due to memory failure and reporting bias, as well as, for intensity level, subjective differences in experience of intensity. It was not always clear, moreover, to what degree individual activities could have been reported by participants in more than one report category, thus potentially resulting in duplication in the formula we developed to aggregate their reports. In

addition, we based this formula on estimates of reported MET expenditure by activity type obtained from overall population averages. These were derived primarily from American samples of quantities that show substantial individual variation. Thus these estimates may not have been directly applicable to our sample overall and definitely were not uniformly applicable to all individuals within the sample. This likely at least partially explains the low phenotypic correlations between MET and the measures of adiposity in this sample.

How are Adiposity and Physical Activity Linked?

Cycle Fitness and adiposity. Despite these limitations, our results offered insight into possible mechanisms linking adiposity and physical activity. We first discuss those involving Cycle Fitness. In general, greater Cycle Fitness was quite consistently associated with less adiposity no matter the specific measure, as well as appearing to act relatively directly to minimize adiposity. The consistently relatively high shared environmental correlations coupled with little shared environmental variance suggested that the apparently relatively direct effects involved environmental circumstances that differed among families but were experienced similarly by both members of these families whether they were MZ or DZ twins, and that these particular environmental circumstances influenced attention to maintaining both healthy body weight and physical activity, or neither. This implies that everyone would experience these circumstances the same way, that is, direct main effects on means that do not affect variance. An alternate interpretation is that, whatever these environmental circumstances or 'culture' might be, they involve both aerobic fitness and minimal adiposity, and affect everyone to about the same degree. There were several adiposity measures for which the shared environmental correlations ranged effectively from -1 to 1 across the range of Cycle Fitness. These appeared to reflect relatively strong main effects of this kind.

At the same time, environmental circumstances that differed within families appeared to have much less consistent individual effects on adiposity, but these effects appeared to be stronger and thus more individually consistent at higher levels of Cycle Fitness, again no matter the specific measure of adiposity. This appeared to be the case for genetic influences as well, though not as strongly or consistently across measures of adiposity. Here, the presumed mode of action would be suppression of expression of genetic variants involved in development of obesity. Moreover, Body Fat Percent showed the opposite pattern of genetic influence, stronger and more consistent at lower levels of Cycle Fitness. To the extent this was not a statistical artifact, it implied that, at least for this

measure, expression of genetic variants was more strongly suppressed when Cycle Fitness was low, suggesting that suppression of expression of genetic variants protected against development of adiposity instead.

Some of the adiposity measures showed moderation of genetic and/or environmental influences on variance common to Cycle Fitness, while others showed moderation on variance unique to the adiposity measure. The moderating effects on unique variance reflected main effects that suppressed or enhanced expression of genetic variance in the phenotype with level of the moderator. The moderating effects on common variance reflected the fact that the model did not capture nonlinear main effects. That is, it appeared that there were nonlinear main effects rather than gene-environment interaction. Some nonlinear main effects involved Cycle Fitness as phenotype. This suggested that greater adiposity acted to impede physical fitness, to increasing degrees with greater adiposity, particularly when the adiposity was concentrated at the waist. Probably relatedly, other nonlinear main effects involved Lean Mass as phenotype. These suggested that greater physical activity, as assessed by both MET and Cycle Fitness, acted to build Lean Mass, to increasing degrees with greater activity.

All genetic and non-shared environmental correlations, no matter the source of influence, were negative, like the phenotypic correlations, though the genetic and non-shared environmental ones tended to be rather low. The consistency of direction suggested that the various sources of influence appeared to work in concert, if not strongly, in linking greater Cycle Fitness to lower levels of adiposity. The low magnitudes of the genetic correlations indicated that there was little genetically influenced tendency for those less genetically prone to obesity to select environments involving greater physical activity. To the extent this was the case, any genetic influences on tendency to avoid physical activity likely did not contribute directly to obesity. Most of the shared environmental correlations were also consistently negative. There were three partial exceptions to this. For BMI, and Fat and Lean Mass, the shared environmental correlations turned completely positive when Cycle Fitness was high. This appeared to reflect some combination of imprecision of measurement due to the very limited amount of shared environmental variance and the tendencies of these measures to overestimate adiposity when body frame size is large relative to height. The latter could be the case, for example, if those with larger body frame relative to height tend to gain relatively more muscle bulk with greater aerobic fitness than those with smaller body frame relative to height. There was little or

no evidence that any of the moderating effects we observed could have been due instead to nonlinear main effects.

The patterns we observed were strongest and most consistent for BMI, WSR, and Fat Mass and weakest and least consistent for WHR and Body Fat Percent. As noted above, BMI tends to be a poorer indicator of adiposity in those with larger body frames relative to height, especially those with greater relative muscle (lean) mass. WSR tends also to be a poorer measure of adiposity in those with greater waist size relative to height, though especially so in those for whom waist size is due to fat mass around the waist rather than those with overall large bone structure relative to height. Thus measurement distortions involving inconsistencies of treatment of body frame and relative muscle mass in the measures of adiposity may tend to exaggerate apparent variance moderation effects. Such measurement distortions may also be the reason that moderation of genetic influences on Body Fat Percent by Cycle Fitness differed from those in the other adiposity measures.

The links between Cycle Fitness and adiposity appeared to be reciprocal. That is, the various measures of adiposity appeared to affect levels of and variance in Cycle Fitness in ways very similar to those of Cycle Fitness on the measures of adiposity. This suggests that, as it develops and becomes greater, people respond increasingly similarly through genetic and non-shared environmental pathways in limiting their physical activity. At the same time, with the exception of WHR, consistent with Cycle Fitness' effects on adiposity, there was evidence that environmental circumstances that differed between families but not within families had the same effects on Cycle Fitness in everyone. These effects were strongest for WSR and weakest for Body Fat Percent, again suggesting that the ways in which the various adiposity measures do not accurately reflect any common concept of adiposity may contribute substantially to the appearance of variance-moderating effects.

MET and adiposity. The patterns involving MET were generally similar to those involving Cycle Fitness, but much less strong. This was likely due to greater imprecision in the MET measure as an indicator of actual physical activity, as well as to inherent differences between physical fitness and habitual physical activity that may be differently associated with obesity. It would be interesting, however, to develop and use more objective and accurate measures of MET such as pace counters and heart rate monitors to see if this would lead to results more similar to those we obtained for Cycle Fitness. An alternative possibility is that the much less dramatic results we obtained for MET indicate

that it is fitness level rather than present activity level that is more closely associated with obesity. This could be the case, for example, if aerobic fitness more accurately reflects long-term patterns of exercise and diet and it is such long-term patterns that are reliably linked to obesity rather than activity levels assessed over relatively short terms. If this were the case, if, for example, most of our currently obese population were to be mobilized pretty much at the same time to exercise to the same degree, any presently existing association between current activity level and obesity might vanish.

One difference between MET and Cycle Fitness results was that, though they remained low, genetic correlations between MET and the various measures of adiposity were positive instead of negative as they were for Cycle Fitness and adiposity. This of course suggested that genetic influences common to MET and adiposity worked to counteract shared and non-shared environmental influences in limiting adiposity with greater physical activity, though not strongly so. The best explanation for this is likely again confounding of body frame size relative to height with relative body fat in some of the adiposity measures, as the most strongly positive genetic correlation was between MET and Lean Body Mass and the least such correlation was between MET and Body Fat Percent.

Conclusions and Suggestions for Future Research

We examined mean effects and moderating effects on variance by two measures of physical activity on six measures of adiposity, as well as the reciprocal effects. Overall results were consistent with prior studies in indicating suppression of variance in adiposity with higher levels of physical activity, but extended those studies, providing more specific insight into the manners in which this takes place and relative strengths and weaknesses of the various construct measures. The variance suppression appeared to take place through both genetic and environmental pathways, but some portion of the mean effects appeared to result from reciprocal influences of environmental circumstances that differed among families but not between individuals within the same family. This suggested that, to some degree, the reciprocal effects are uniform in everyone. At the same time, some of the moderating effects on variance appeared to be due to the particular ways in which the individual measures of adiposity tend to be biased for individuals with particular body characteristics, as well as measurement differences and sources of inaccuracy in measures of physical activity. This suggests a need to avoid reliance on single measures of either in attempting to understand the pathways involved in their linkages, and constraint in interpreting results when only single measures

have been used, especially because it appeared that different measures shared genetic influences to varying degrees.

Future studies can make use of these results to explore the specific environmental circumstances involving physical activity to which everyone's tendencies toward obesity may be the same, as well as those environmental circumstances to which people's obesity levels tend to respond differently. Those to which everyone responds the same may be particularly valuable as intervention targets, as many intervention programs lose first those participants who respond least, often because they receive less positive feedback than others around them. Too often these are the participants who need the intervention most.

The low genetic correlations indicated rather little genetically influenced selection into environments of greater physical activity by those less prone to obesity. This suggests that whatever genetic influences there may be on tendency to avoid physical activity, they are unlikely to be tied very closely to tendency to obesity. Thus it may be possible to make the general idea of some form of physical activity in pursuit of health seem pretty much equally attractive to everyone, though the specific forms of activity that appeal may not be at all the same.

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Table I
Descriptive Statistics

	N	Minimum	Maximum	Mean	Standard Deviation
<u>All</u>					
Age	1512	18	67	37.8	10.9
Height (cm)	1510	149	204	172.9	9.2
Weight (kg)	1510	40.2	125.0	73.16	12.96
Body Mass Index	1510	16.1	43.7	24.40	3.51
Waist-Hip Ratio	1509	0.65	1.11	0.867	0.085
Waist Stature Ratio	1509	0.35	0.72	0.484	0.057
Body Fat Percent	1039	5.2	51.1	25.79	7.75
Fat Mass (kg)	1039	3.0	61.6	19.04	7.67
Lean Mass (kg)	1039	35.0	80.4	53.63	9.50
Cycle Fitness Test Rating	1248	14.7	57.7	34.34	8.10
Daily Total MET Expenditure	1244	1475	6000	3283.1	928.9
Daily MET Expenditure in Sport	1512	0	1800	104.4	170.2
Daily MET Expenditure Walking	1512	0	825	208.1	177.5
Daily MET Expenditure Cycling	1512	0	1050	83.4	113.4
Other Daily MET Expenditure	1244	1440	5130	2801.9	772.2
<u>Women</u>					
Age	783	18	67	37.5	10.7
Height (cm)	781	149	189	166.6	6.2
Weight (kg)	781	40.2	120.5	66.5	11.2
Body Mass Index	781	16.1	43.7	23.966	3.827
Waist-Hip Ratio	781	0.65	1.02	0.812	0.058
Waist Stature Ratio	781	0.35	0.72	0.472	0.058
Body Fat Percent	561	8.5	51.1	29.69	7.00
Fat Mass (kg)	561	3.4	61.6	20.47	8.15
Lean Mass (kg)	561	35.0	63.3	46.20	4.38
Cycle Fitness Test Rating	625	14.7	51.1	31.04	6.76
Daily Total MET Expenditure	635	1509	5999	3097.7	801.0
Daily MET Expenditure in Sport	783	0	1200	87.3	151.1
Daily MET Expenditure Walking	783	0	825	197.7	174.6
Daily MET Expenditure Cycling	783	0	675	84.4	110.5
Other Daily MET Expenditure	635	1440	5130	2642.2	638.4
<u>Men</u>					
Age	729	18	63	38.0	11.1
Height (cm)	729	160	204	179.7	6.8
Weight (kg)	729	55.5	125.0	80.27	10.76
Body Mass Index	729	17.7	40.4	24.86	3.08
Waist-Hip Ratio	728	0.74	1.11	0.927	0.066
Waist Stature Ratio	728	0.39	0.70	0.498	0.053
Body Fat Percent	478	5.2	36.8	21.21	5.87
Fat Mass (kg)	478	3.0	44.8	17.37	6.70
Lean Mass (kg)	478	46.5	80.4	62.34	5.76

Cycle Fitness Test Rating	623	16.4	57.7	37.66	8.00
Daily Total MET Expenditure	609	1475	6000	3476.4	1010.7
Daily MET Expenditure in Sport	729	0	1800	122.8	186.9
Daily MET Expenditure Walking	729	0	825	219.4	180.1
Daily MET Expenditure Cycling	729	0	1050	82.3	116.4
Other Daily MET Expenditure	609	1440	5130	2968.4	860.0

Table II
Correlations Among Study Variables

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Age	1.000	.022	-.119	.135	.258	.201	.382	.362	.306	-.104	-.460	-.139	-.135	.033	-.161	-.100
2. Sex		1.000	.710	.530	.128	.681	.225	-.545	-.201	.847	.408	.204	.104	.061	-.010	.211
3. Height			1.000	.605	.002	.436	-.001	-.435	-.082	.869	.386	.155	.141	.026	.051	.139
4. Weight				1.000	.793	.579	.706	.304	.679	.805	-.127	.091	.048	.002	-.017	.104
5. BMI					1.000	.390	.891	.705	.905	.349	-.448	.004	-.043	-.014	-.054	.030
6. WHR						1.000	.605	-.094	.174	.622	.007	.110	-.052	-.075	-.123	.148
7. WSR							1.000	.612	.788	.312	-.473	-.046	-.102	.016	-.080	-.003
8. Body Fat %								1.000	.892	-.309	-.718	-.203	-.125	-.083	-.082	-.188
9. Fat Mass									1.000	.111	-.619	-.132	-.086	-.062	-.071	-.117
10. Lean Mass										1.000	.310	.213	.130	.064	.028	.210
11. Cycle Fit											1.000	.315	.331	.044	.303	.245
12. Total MET												1.000	.465	.480	.227	.958
13. Sport MET													1.000	.204	.197	.296
14. Walk MET														1.000	.252	.337
15. Cycle MET															1.000	.077
16. Other MET																1.000

Note: Raw variable correlations above the diagonal; age-sex adjusted correlations below. See text and Table 1 for full variable definitions. Correlations greater than |.05| were significant at $p < .05$, without adjustment for multiple testing.

Table III
Genetic and Environmental Correlations between Adiposity Measures

	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
Genetic Correlations						
1. BMI	1.00					
2. WHR	.36	1.00				
3. WSR	.88	.65	1.00			
4. Body Fat %	.92	.27	.86	1.00		
5. Fat Mass	.93	.28	.80	.95	1.00	
6. Lean Mass	.51	.10	.26	.41	.63	1.00
Shared Environmental Correlations						
1. BMI	1.00					
2. WHR	.30	1.00				
3. WSR	1.00	.29	1.00			
4. Body Fat %	.97	.05	.96	1.00		
5. Fat Mass	.95	.14	.94	.98	1.00	
6. Lean Mass	.45	.78	.42	.30	.47	1.00
Non-Shared Environmental Correlations						
1. BMI	1.00					
2. WHR	.52	1.00				
3. WSR	.89	.75	1.00			
4. Body Fat %	.91	.51	.82	1.00		
5. Fat Mass	.98	.54	.88	.95	1.00	
6. Lean Mass	.75	.41	.64	.57	.71	1.00

Note: Genetic correlations in excess of .33 were significant. Shared environmental correlations in excess of .50 were significant. All non-shared environmental correlations were significant.

Table IV
Twin Correlations of Study Variables

	MZ (N=311)	95% Confidence	DZ (N=445)	95% Confidence
BMI	.702	(.635-.760)	.417	(.343-.482)
WHR	.642	(.575-.707)	.501	(.422-.574)
WSR	.615	(.529-.610)	.369	(.267-.456)
Body Fat %	.661	(.562-.748)	.355	(.232-.467)
Fat Mass	.650	(.531-.748)	.405	(.281-.513)
Lean Mass	.836	(.793-.866)	.455	(.367-.536)
Cycle Fit	.658	(.582-.726)	.433	(.351-.507)
Total MET	.394	(.293-.499)	.162	(.082-.249)

Note: Correlations are intraclass. See text and Table I for full variable definitions. Ns are pairs. Variables are age-sex adjusted.

Table V
Fit Statistics for Models Involving Cycle Fitness

	BMI	WHR	WSR	Body Fat %	Fat Mass	Lean Mass	Total MET
<u>Cycle Fitness as Moderator</u>							
Full Model							
-2 Log-likelihood	5957.6	6370.0	3461.2	5531.6	5401.1	5681.2	3814.5
Degrees of Freedom	2459	2458	1427	2214	2214	2214	1401
AIC	1039.6	1454.0	607.2	1103.5	973.1	1253.2	1012.5
Sample-Size Adjusted BIC	-1021.1	-813.8	-207.5	-835.6	-900.8	-760.8	4.4
No-Interaction Model							
Δ -2 Log-likelihood (Δ df)	174.2 (3)	14.0 (3)	79.4 (3)	30.2 (2)	19.9 (5)	24.7 (1)	0 (0)
p of test to Best Model	<.001	.003	<.001	<.001	.001	<.001	1.000
AIC	1204.6	1461.7	665.3	1123.0	1094.9	1274.9	1005.5
Sample-Size Adjusted BIC	-942.4	-813.2	-180.6	-829.6	-843.7	-753.7	-1.2
Best-Fitting Model							
Δ -2 Log-likelihood (Δ df)	2.8 (3)	5.7 (3)	.7 (3)	1.2 (4)	0.1 (1)	8.9 (5)	5.0 (6)
p of test to Full Model	.423	.127	.873	.878	.752	.113	.544
AIC	1036.4	1453.7	601.9	1096.8	971.1	1252.1	1005.5
Sample-Size Adjusted BIC	-1024.6	-815.3	-211.2	-840.5	-902.4	-764.4	-1.2
Moderating Parameters	Au, Cc, Eu	Ac, Cc, Eu	Cu, Ec, Eu	Ac, Eu	All but Ec	Cc	None
Competing Nonlinear?	No	No	No	No	No	Yes	No
<u>Cycle Fitness as Phenotype</u>							
Full Model							
-2 Log-likelihood (df)	6874.3	7119.0	6902.1	4740.2	4724.0	4831.0	5955.8
Degrees of Freedom	2741	2737	2737	1893	1893	1893	2181
AIC	1392.3	1645.0	1428.1	954.2	938.0	1045.0	1593.8
Sample-Size Adjusted BIC	-1292.9	-1161.8	-1270.3	-481.0	-489.1	-435.6	-575.1
No-Interaction Model							
Δ -2 Log-likelihood (Δ df)	19.0 (2)	5.5 (2)	16.3 (2)	21.3 (2)	10.5 (1)	15.4 (3)	0 (0)
p of test to Best Model	<.001	.064	<.001	<.001	.001	.002	1.000
AIC	1402.7	1641.8	1436.4	964.8	1419.5	1053.6	1585.3
Sample-Size Adjusted BIC	-1292.0	-1167.8	-1270.5	-478.8	-268.6	-434.4	-583.1
Best-Fitting Model							
Δ -2 Log-likelihood (Δ df)	3.4 (4)	1.3 (4)	3.9 (4)	1.3 (4)	4.1 (5)	3.1 (6)	3.5 (6)
p of test to Full Model	.493	.861	.420	.861	.966	.796	.744
AIC	1387.7	1638.3	1424.0	947.5	1419.5	1042.1	1585.3
Sample-Size Adjusted BIC	-1298.1	-1168.0	-1275.2	-486.4	-268.6	-439.1	-583.1
Moderating Parameters	Au, Eu	Ac, Ec	Au, Cc	Ac, Au	Au	Cc, Ec	None
Competing Nonlinear?	No	Yes	Yes	Yes	No	No	No

Note: Δ -2 Loglikelihood is with respect to full model. AIC is Akaike Information Criterion; BIC is Bayesian Information Criterion. BMI is Body Mass Index; WHR is waist-hip ratio; WSR is waist-stature ratio; MET is metabolic equivalent. For moderating parameters, Ac refers to moderation of genetic influences common to moderator and outcome (b_1), Au to moderation of genetic influences unique to the outcome (b_4), Cc to common shared environmental influences (b_2), Cu to unique shared environmental influences (b_5), Ec to common nonshared environmental influences

fluences unique to the outcome (b_4), Cc to common shared environmental influences (b_2), Cu to unique shared environmental influences (b_5), Ec to common nonshared environmental influences (b_3) and Eu to unique nonshared environmental influences (b_6). Competing Nonlinear? refers to whether a nonlinear main effects model could also explain the data. If not listed as a moderating parameter for the best-fitting model, moderating parameters were fixed to 0.

Table VI
Fit Statistics for Models Involving MET

	BMI	WHR	WSR	Body Fat %	Fat Mass	Lean Mass
<u>MET as Moderator</u>						
Full Model						
-2 Log-likelihood	6712.4	6762.6	6798.3	6228.4	6187.3	6068.8
Degrees of Freedom (df)	2471	2471	2471	2266	2266	2266
AIC	1770.4	1820.6	1856.3	1696.4	1655.3	1554.8
Sample-Size Adjusted BIC	-669.2	-644.1	-626.3	-577.2	-597.8	-655.0
No-Interaction Model						
Δ -2 Log-likelihood (Δ df)	13.1 (2)	0 (0)	0 (0)	5.9 (1)	10.0 (1)	4.5 (1)
p of test to Best Model	.001	1.000	1.000	.015	.002	.034
AIC	1771.2	1812.1	1853.6	1691.4	1656.8	1548.9
Sample-Size Adjusted BIC	-672.3	-652.1	-631.4	-583.5	-600.8	-654.7
Best-Fitting Model						
Δ -2 Log-likelihood (Δ df)	.2 (4)	3.5 (6)	9.3 (6)	1.1 (5)	3.0 (5)	20.3 (5)
p of test to Full Model	.995	.744	.157	.954	.700	.480
AIC	1762.6	1812.1	1853.6	1687.5	1648.3	1547.1
Sample-Size Adjusted BIC	-675.6	-652.1	-631.4	-584.8	-604.4	-655.0
Moderating Parameters	Au, Eu	None	None	Au	Au	Cc
Competing Nonlinear?	No	No	No	No	No	Yes
<u>MET as Phenotype</u>						
Full Model						
-2 Log-likelihood (df)	7369.5	7442.3	7510.4	5309.3	5282.1	5149.5
Degrees of Freedom (df)	2737	2735	2735	1927	1927	1927
AIC	1895.5	1972.3	2040.4	1455.3	1428.1	1295.5
Sample-Size Adjusted BIC	-1038.4	-996.7	-962.6	-247.7	-261.3	-327.6
No-Interaction Model						
Δ -2 Log-likelihood (Δ df)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5.6 (1)
p of test to Best Model	1.000	1.000	1.000	1.000	1.000	.018
AIC	1895.1	1962.7	3032.0	1447.8	1419.5	1295.6
Sample-Size Adjusted BIC	-1042.9	-1005.8	-971.2	-254.4	-268.6	-330.6
Best-Fitting Model						
Δ -2 Log-likelihood (Δ df)	11.6 (6)	2.4 (6)	4.0 (6)	6.5 (6)	1.4 (6)	6.5 (5)
p of test to Full Model	.072	.879	.677	.370	.966	.370
AIC	1895.1	1962.7	3032.0	1447.8	1419.5	1292.0
Sample-Size Adjusted BIC	-1042.9	-1005.8	-971.2	-254.4	-268.6	-331.9
Moderating Parameters	None	None	None	None	None	Cu
Competing Nonlinear?	No	No	No	No	No	No

Note: Δ -2 Loglikelihood is with respect to full model. AIC is Akaike Information Criterion. BIC is Bayesian Information Criterion. BMI is Body Mass Index; WHR is waist-

hip ratio WSR is waist-stature ratio; MET is metabolic equivalent. For moderating parameters, Ac refers to moderation of genetic influences common to moderator and outcome (b_1), Au to moderations of genetic influences unique to the outcome (b_4), Cc to common shared environmental influences (b_2), Cu to unique shared environmental influences (b_5), Ec to common nonshared environmental influences (b_3), and Eu to unique nonshared environmental influences (b_6). Competing Nonlinear? refers to whether a nonlinear main effects model could also explain the data.

Table VII
Estimated Genetic and Environmental Influences on MET

Potential Moderator	Estimated Genetic Variance	Estimated Shared Environ. Variance	Estimated Nonshared Environ. Variance	Estimated Genetic Correlation	Estimated Shared Environ. Correlation	Estimated Nonshared Environ. Correlation
BMI	.34	.03	.63	.29	-1.00	-.14
WHR	.36	.01	.63	.30	-1.00	-.09
WSR	.35	.02	.63	.19	-1.00	-.14
Body Fat %	.39	.00	.61	.03	undefined	-.16
Fat Mass	.38	.01	.61	.13	-1.00	-.18
Lean Mass	.27	Overall .07	.64	.25	.19-1.00	-.05

Note: Only Lean Mass moderated variance. Under the best-fitting model, shared environmental variance ranged from .04 at 2SD below mean MET to .45 at 2SD above mean MET. At mean MET, it was .05.

Figure captions:

Figure 1 - Model of moderation of genetic and environmental influences on obesity as moderated by exercise for one twin. A refers to genetic influences, C to shared environmental influences, and E to nonshared environmental influences. Exercise is represented as a triangle because we conceptualize it as an environmental moderating variable with respect to Obesity. Obesity may be influenced by all six of the paths shown, and the extent of these influences may vary linearly with Exercise, noted by M in the paths above. The genetic and environmental paths influencing Exercise are also shown in the figure, but not labeled.

Figure 2 – Moderating effects of Cycle Fitness on measures of obesity. A refers to genetic influences, C to shared environmental influences, E to non-shared environmental influences. The figure is based on results from the best-fitting models summarized in the top panel of Table IV.

Figure 3 – Means of obesity measures and corresponding genetic and shared and non-shared environmental correlations between the measures of obesity and Cycle Fitness, as functions of Cycle Fitness. r_A refers to genetic correlation, r_C to shared environmental correlation, E to non-shared environmental correlation. The figure is based on results from the best-fitting models summarized in the top panel of Table IV.

Figure 4 – Moderating effects of measures of obesity on Cycle Fitness. A refers to genetic influences, C to shared environmental influences, E to non-shared environmental influences. The figure is based on results from the best-fitting models summarized in the bottom panel of Table IV.

Figure 5 – Means of obesity measures and corresponding genetic and shared and non-shared environmental correlations between Cycle Fitness and the measures of obesity, as functions of the obesity measures. r_A refers to genetic correlation, r_C to shared environmental correlation, E to non-shared environmental correlation. The figure is based on results from the best-fitting models summarized in the bottom panel of Table IV.

Figure 6 - Moderating effects of MET on measures of obesity. A refers to genetic influences, C to shared environmental influences, E to non-shared environmental influences. The figure is based on results from the best-fitting models summarized in the top panel of Table V.

Figure 7 – Means of obesity measures and corresponding genetic and shared and non-shared environmental correlations between the measures of obesity and MET, as functions of MET, where variance-moderating effects were significant. r_A refers to genetic correlation, r_C to shared environmental correlation, E to non-shared environmental correlation. The figure is based on results from the best-fitting models summarized in the top panel of Table V.

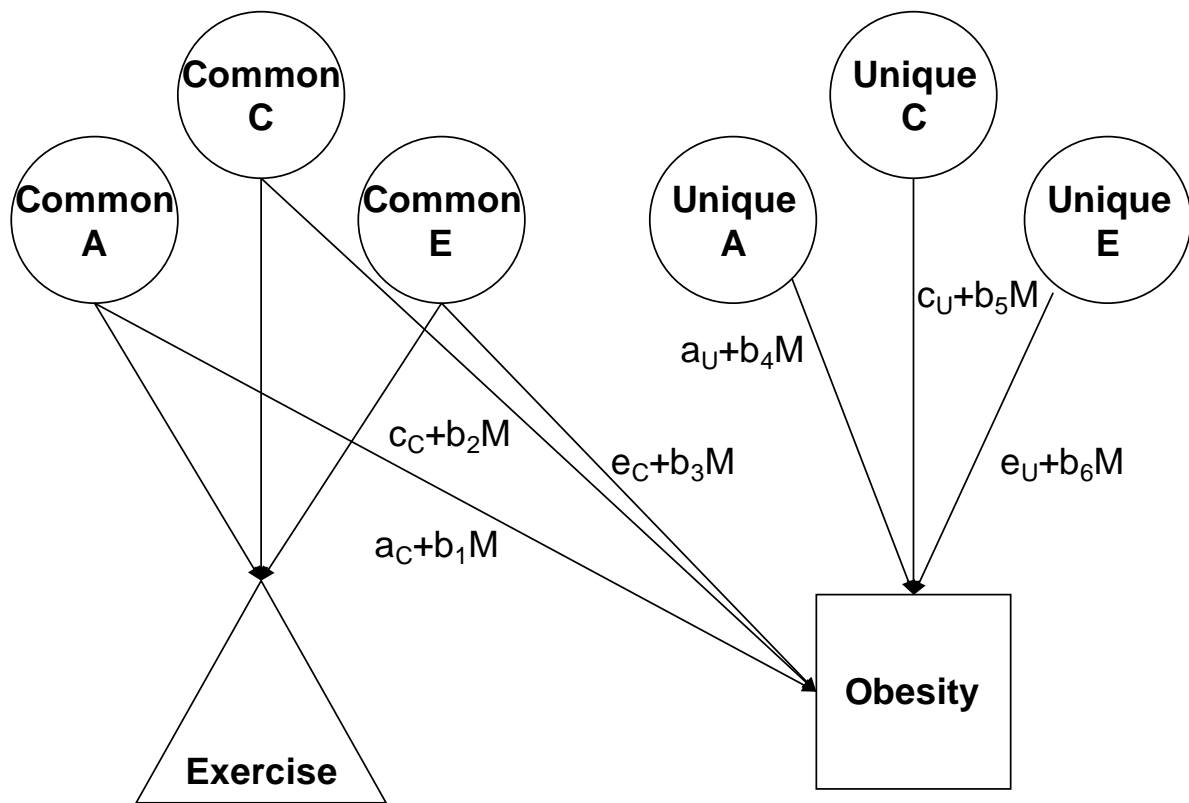


Figure 1

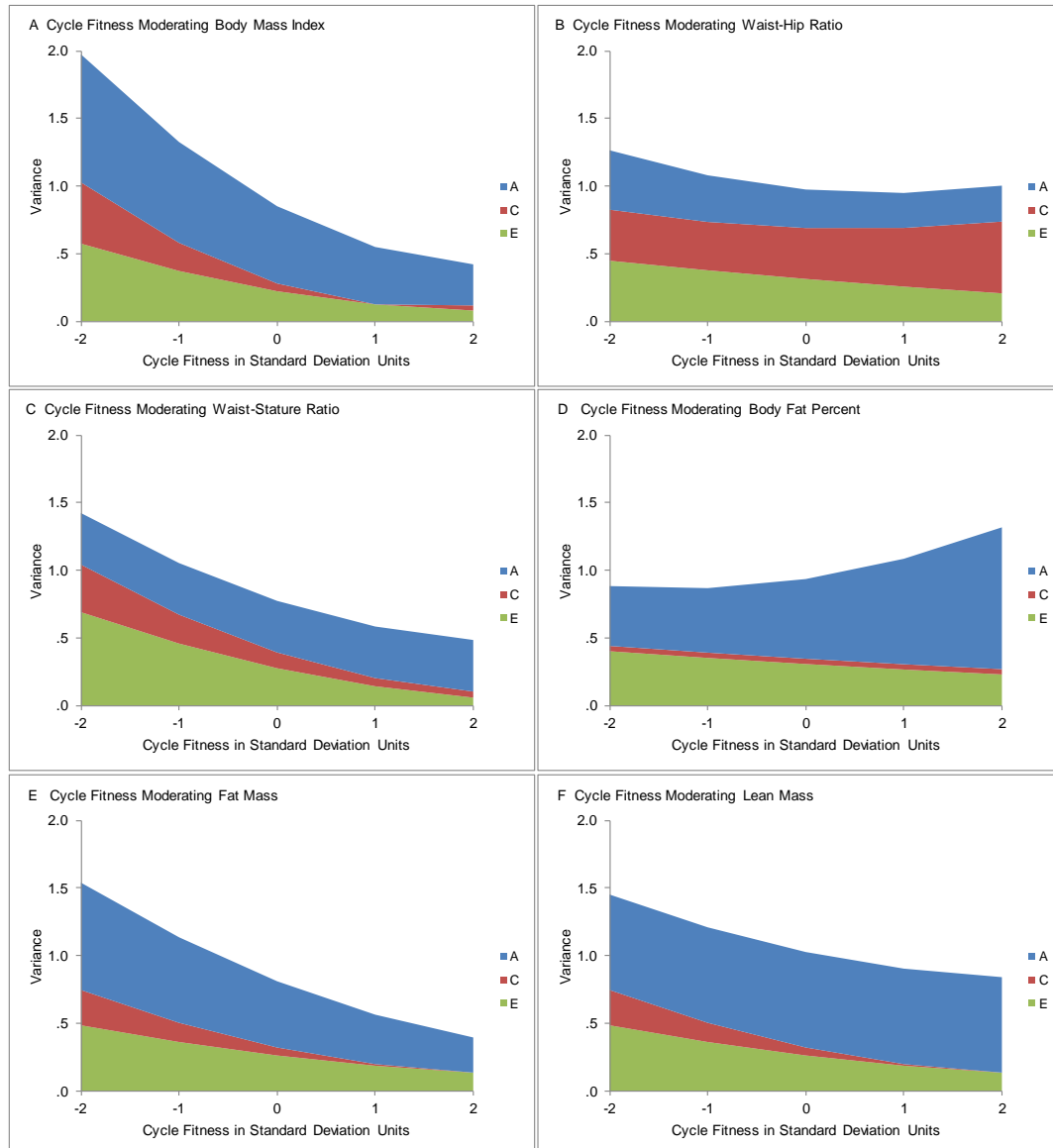


Figure 2

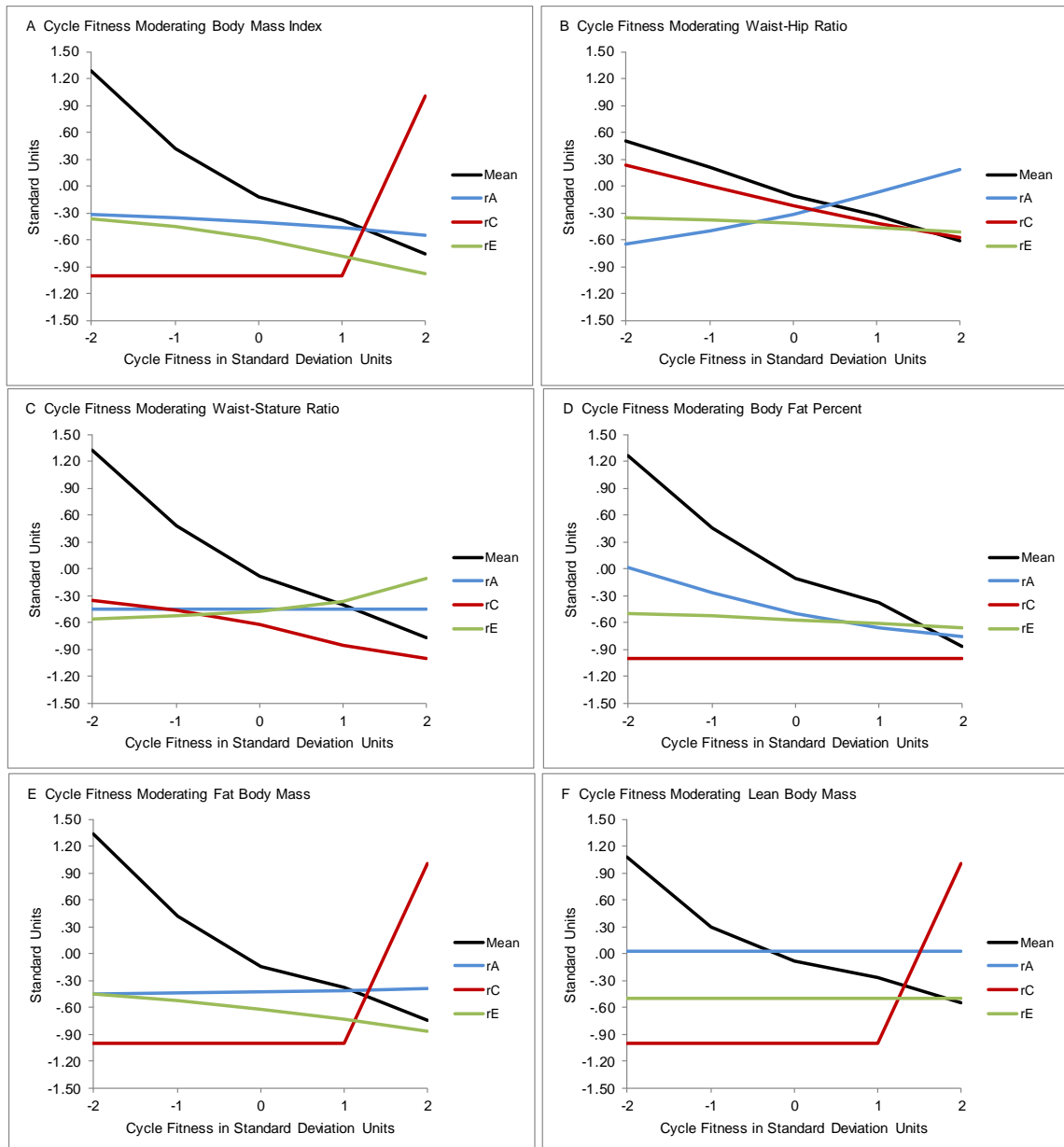


Figure 3

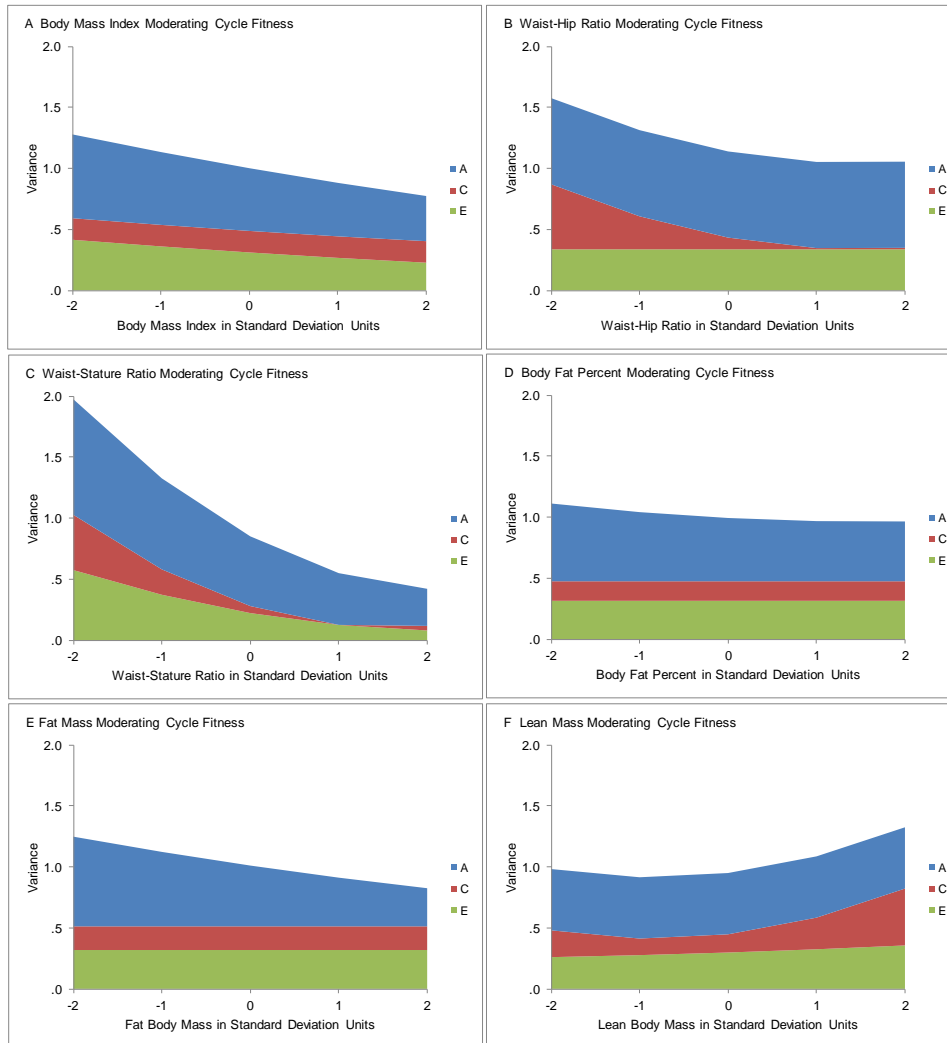


Figure 4

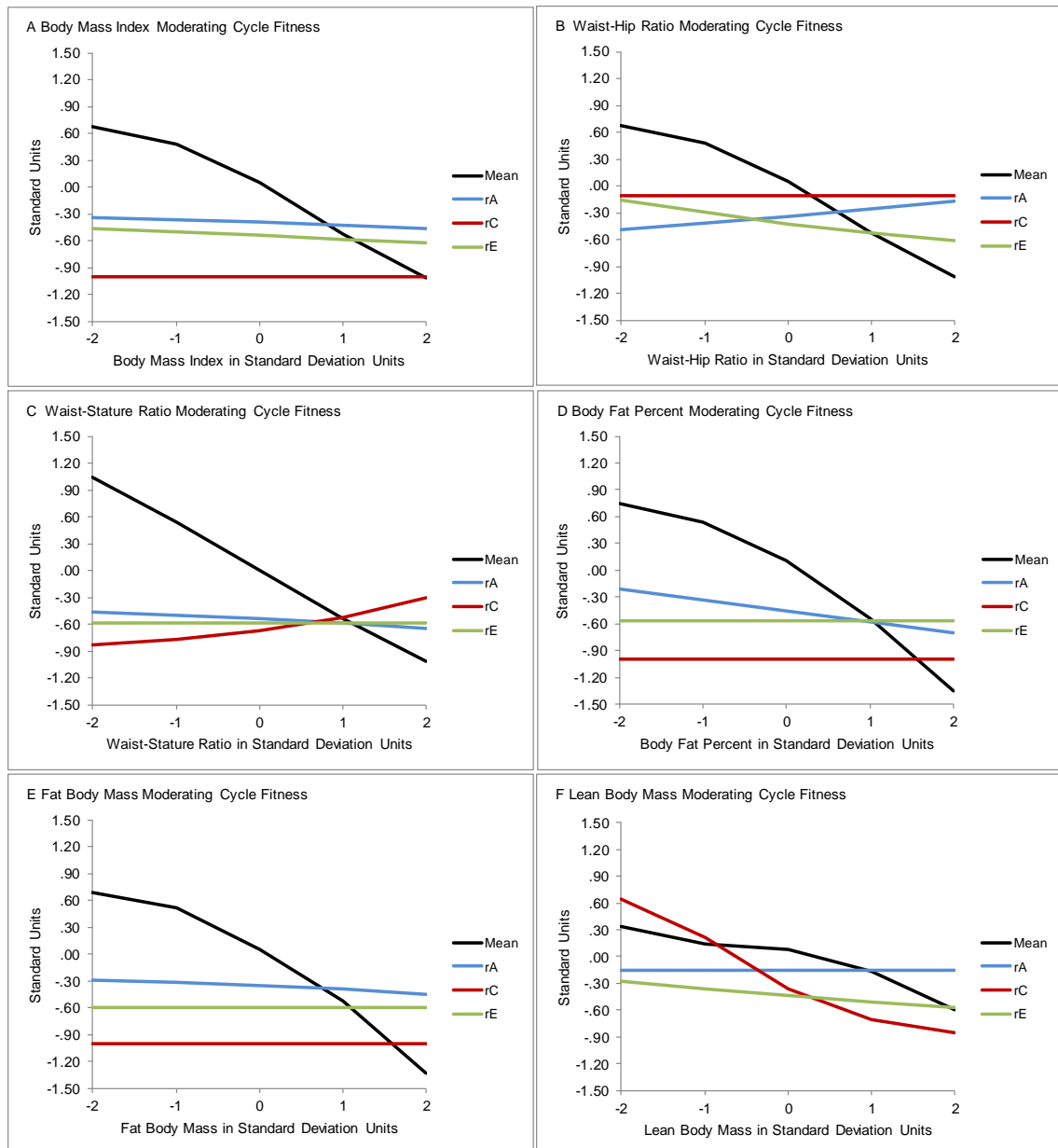


Figure 5

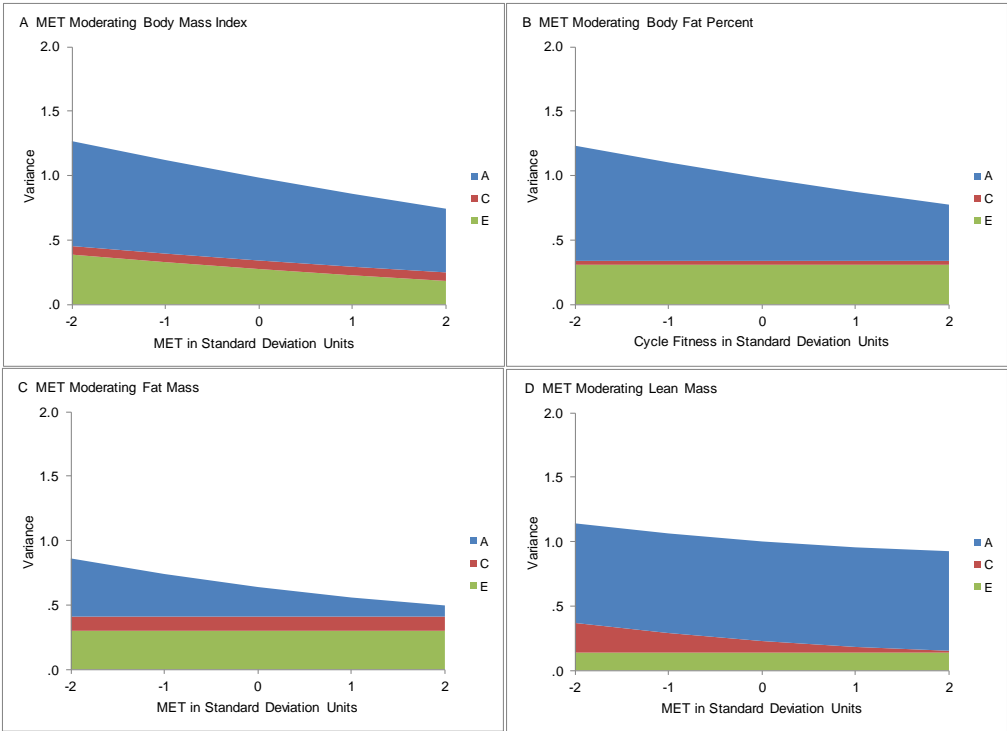


Figure 6

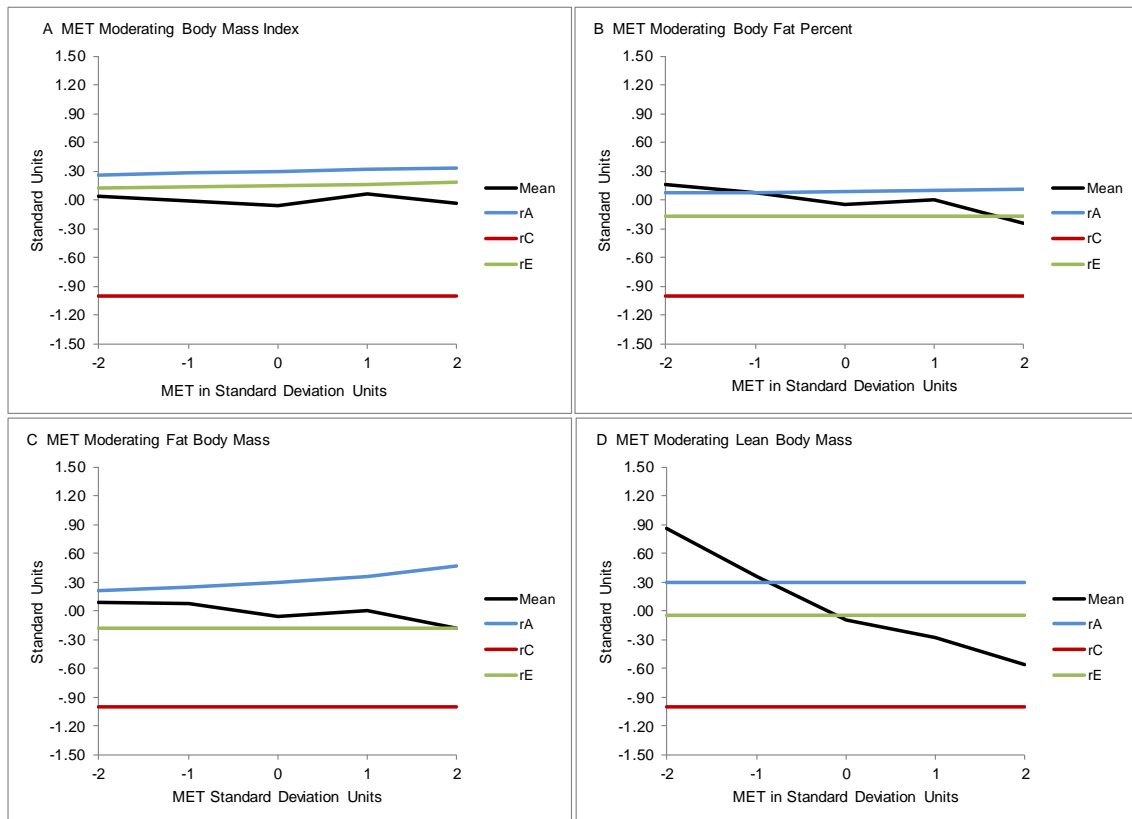


Figure 7